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## Review article

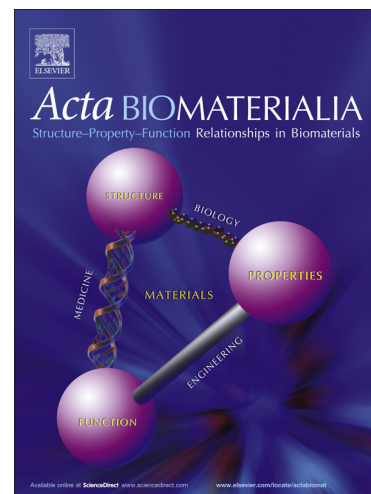
Glass-ceramics for cancer treatment: So close, or yet so far?

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## Glass-ceramics for cancer treatment: So close, or yet so far?

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**Abstract**

After years of research on the ability of glass-ceramics in bone regeneration, this family of biomaterials has shown revolutionary potentials in a couple of emerging applications such as cancer treatment. Although glass-ceramics have not yet reached their actual potential in cancer therapy, the relevant research activity is significantly growing in this field. It has been projected that this idea and the advent of magnetic bioactive glass-ceramics and mesoporous bioactive glasses could result in major future developments in the field of cancer. Undoubtedly, this strategy needs further developments to better answer the critical questions essential for the clinical usage. This review aims to address the existing research developments on glass-ceramics for cancer treatment, starting with the current status and moving to the future advances.

**Keywords:** Glass-ceramic; Bioactive glass; Biomaterials; Ferrimagnetism; Hyperthermia; Cancer; Magnetite

## 1. Introduction

Cancer is among one of the most problematic diseases in the medical investigation of our time, in which the cells divide uncontrollably and destroy tissues [1]. It is known as a challenging illness to treat because of the fact that the existing cure choices are incomplete and, somehow, the suitable diagnosis and prognosis are complex [2]. There are many ways to treat cancer tumors including surgery, radiotherapy, chemotherapy, and immunotherapy. However, all these strategies have shown risky side effects [3-5]. Therefore, much effort has been dedicated to the discovery of new methods (noninvasive and minimally invasive) for tumor diagnosis and treatment [6]. Hyperthermia therapy is a type of medical treatment to destroy tumors at higher temperatures [7].

It is known that there is always lack of sufficient blood vessels in cancerous tumors. This irregular network of vessels is a weak platform for cancerous cells which can be destructed at higher temperatures (around 43 °C) due to hemorrhage, stasis and vascular occlusion. This elevated temperature is not harmful to the surrounding tissues since the generated heat mostly transfers through a normal blood vessel system [8, 9]. There have been several reports on the effect of hyperthermia on the pH of tumors. It is known that this process is able to reduce the pH value in tumors as a result of vascular occlusion. This pH value reduction can potentially enhance the heat sensitivity of tumor cells [7, 10, 11].

Altogether, hyperthermia can be considered as an alternative cancer treatment process [12]. Several methods such as hot water, radiofrequency, infrared rays, ultraviolet rays, and microwaves, etc. have been used in hyperthermia treatment [10]. One of the drawbacks of these approaches is the difficulty of homogenous heating of the cancer tumor [13]. Among the

methods of hyperthermia, magnetic induction technique is an effective approach to heat the deep-seated tumors locally and effectively. There is a range of magnetic materials that can be used for the destruction of cancer cells, as a result of an external magnetic stimulation. Several biomaterials presenting this ability have been developed, among which magnetic glass-ceramics have shown promising outcomes [7, 11]. Numerous types and compositions of glass-ceramics have been developed and applied with reference to the treatment of different types of cancer cells [14, 15]. It is worth mentioning that some classes of magnetic glass-ceramics present anti-cancer magnetic features as well as bioactivity at the same time. These glass-ceramics are implanted near the tumorous bone tissue, without the risk of displacement by biological fluids in the body. Under an external altering magnetic field, the aforementioned glass-ceramics start to destroy cancer cells through the hyperthermia effect. Additionally, they can directly bond to the tumorous bone as a result of bioactivity which can further stimulate bone regeneration [16, 17]. Besides magnetic glass-ceramics, mesoporous bioactive glasses have also achieved much attention due to their possibility to carry anticancer drugs into the tumor site [18].

This review article aims to summarize the pros and cons of glass-ceramics in cancer treatment strategy. It is suggested that magnetic bioactive glass-ceramics and mesoporous bioactive glasses are able to tackle cancerous cells through different mechanisms of action. Apart from heat generating ability of magnetic bioactive glass-ceramics and anti-cancer drug delivery capability of mesoporous bioactive glasses, there are a few reports on the spontaneous ability of this class of materials for tissue regeneration. On this point, the literature has been reviewed to precisely evaluate the existing facts on these synthetic biomaterials.

## 2. Theoretical background and definitions

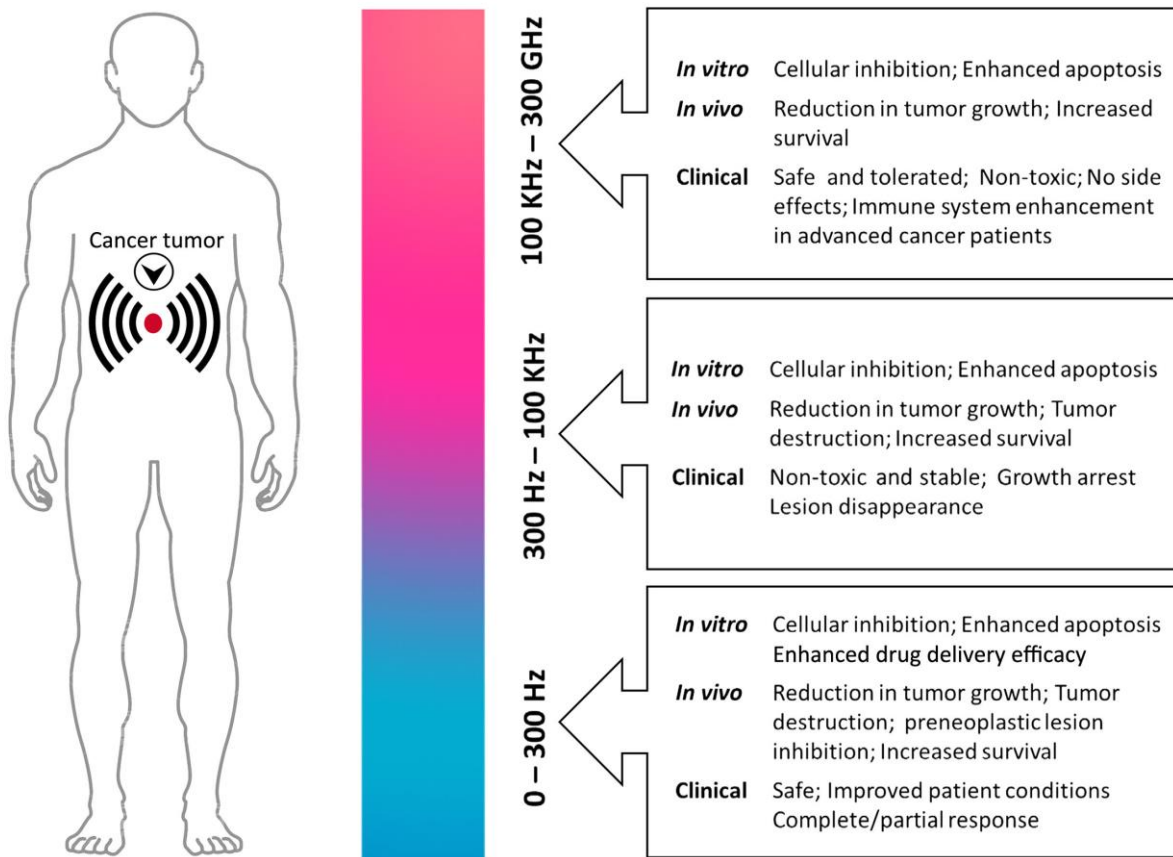
### 2.1. Basic concepts in magnetism

Magnetism arises from the presence of magnetic dipoles in solid materials. When a magnetic material is subjected to a magnetic field, magnetic dipoles having south and north poles tend to align themselves with the applied field. Depending on the reaction of magnetic dipoles to the external magnetic field, materials can be categorized as diamagnetic, paramagnetic, ferromagnetic, antiferromagnetic and ferromagnetic [19].

Ferromagnetic and ferrimagnetic materials adopt permanent magnetization after subjection to an altering external field. In ferromagnetic materials, regions in which magnetic dipoles are more aligned in the same direction with the applied field, start to develop to the detriment of less aligned ones, when exposed to an external AC magnetic field. When the magnetic field is disconnected, some of the aligned regions still remain and provide permanent magnetization. In ferrimagnetic materials, neighboring regions contain antiparallel and unequal magnetization which cannot completely compensate for each other. Hence, when the external field is disconnected, a net magnetization still remains, giving the material a permanent magnetization [19].

Among different magnetic materials, ferromagnetic and ferrimagnetic ones are extensively utilized for cancer treatment via a magnetic hyperthermia effect. Fig. 1 summarizes the *in vitro*, *in vivo* and clinical effects of the pulsed magnetic field on cancer cells in a wide frequency range [20]. During exposing to a high frequency altering magnetic field, ferromagnetic and ferrimagnetic materials produce heat owing to the hysteresis effect of the subjected materials. The released heat is greatly influenced by particle size and its distribution. A reduction

in particle size with a homogeneous distribution is preferred since they absorb power, more effectively[19]. As the temperature is increased from 0 K, the magnetization reduces in both ferromagnetic and ferrimagnetic materials [21].



**Fig. 1.** In magnetic hyperthermia, the generated heat mainly originates from eddy currents and hysteresis losses. Altering/pulsed magnetic fields are able to induce small electric currents, in conducting tissues, proportional to the applied frequency. At very high frequencies, induced currents may generate a harmful heat in the tissues. At low frequencies (0–100 KHz), the released heat in the tissues is somewhat negligible, but the induced currents, if sufficiently strong, can possibly stimulate cells through an electrically stimulation mechanism. (partially reprinted with the permission from [20]).

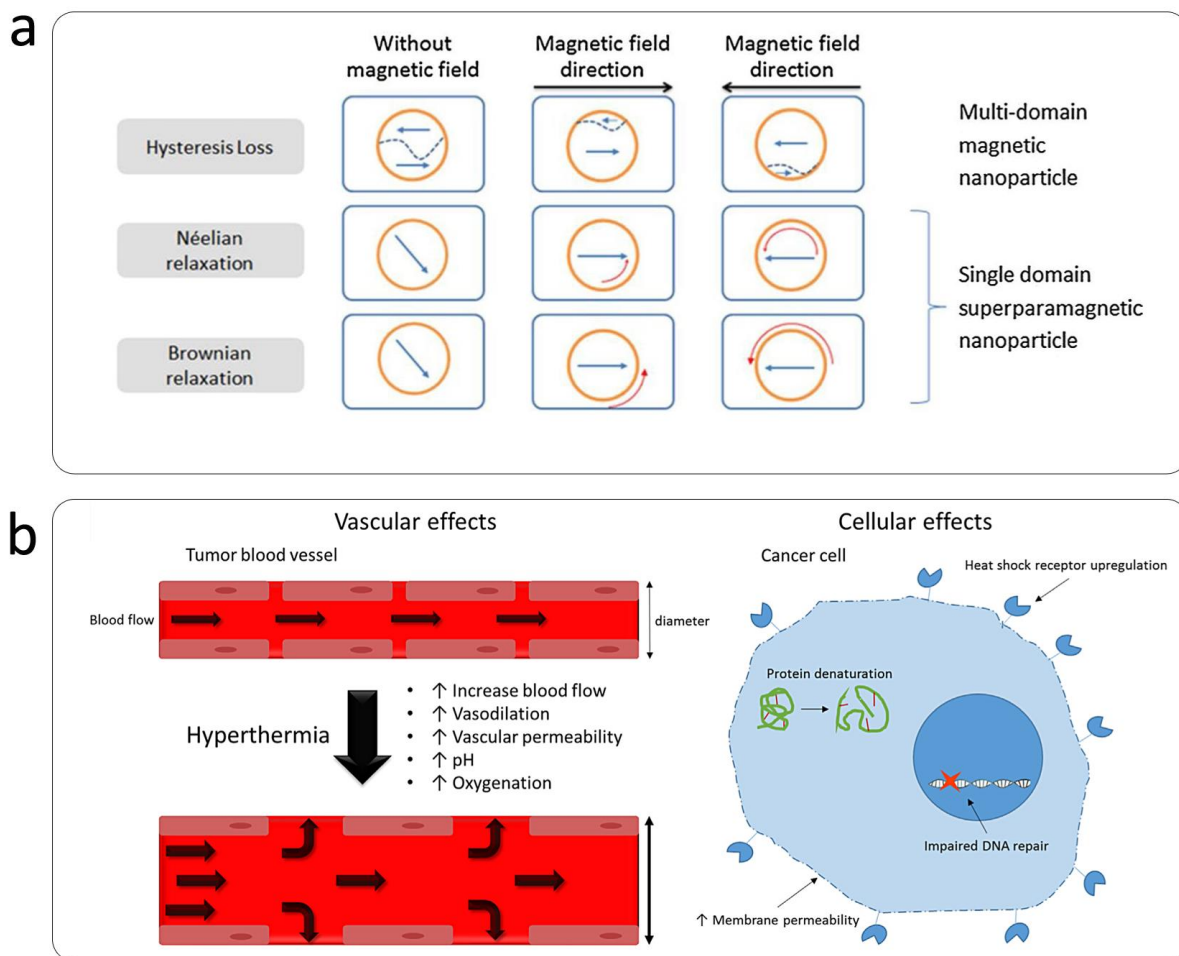
Heat generation in magnetic hyperthermia originates from several heating loss mechanisms. The well-known mechanism is related to the eddy current heat loss occurring in

bulk materials. Eddy current can be induced by an altering magnetic field and is perpendicular to the plane of applied field. This current flowing through the material dissipates energy as the heat loss [22].

In the case of nano-sized materials, the eddy current heating loss is negligible. For particles of micro/nano dimensions, the dominant heating mechanism is hysteresis loss. In this case, heat generation occurs by dissipating thermal energy throughout the magnetic domains of ferromagnetic material. When the particle size is smaller than the superparamagnetic critical diameter, the hysteresis loss is presented in terms of the Néelian and Brownian relaxation (see Fig. 2a). The Néelian relaxation is attributed to the heat generated by rotation of discrete magnetic moments in the magnetic particles; whereas the Brownian relaxation is attributed to the heat generated by physical rotation of particles originating from alignment of magnetic moments with the applied magnetic field [22].

Hyperthermia therapy has been successfully applied along with chemo- or radio-therapy for treatment of primary cancerous tumors, as these tumorous cells are more susceptible to hyperthermic effects. Fig. 2b shows the vascular and cellular effects of hyperthermia on heated tumor tissues. Hyperthermia leads to induce different physiological responses from the heated defected tissues. In view point of vascular effects, these responses comprise increased blood flow, vasodilation, and enhanced permeability. These effects can result in altering of pH as well as microenvironment conditions of tumors. In view point of cellular effects of hyperthermia therapy, several cellular processes such as biomolecular assemblies and cellular mechanisms responsible for onset of acidosis or apoptosis may be disrupted through protein denaturation, aggregation, and DNA cross-linking [23].





**Fig. 2.** (a) Different heat generation mechanisms in magnetic nanoparticles subjected to the altering magnetic field. The short straight arrows show the direction of magnetic moment. The curved arrows show the movement or change of direction, and the dash lines show the domain interfaces in multi-domain magnetic particles. The Néelian relaxation is attributed to the heat generated by rotation of discrete magnetic moments in the magnetic particles; whereas the Brownian relaxation is attributed to the heat generated by physical rotation of particles originating from alignment of magnetic moments with the applied magnetic field. (reprinted with the permission from [22])

(b) Vascular and cellular effects of hyperthermia on heated tumor tissues. Vascular effects comprise increase of blood flow, vascular permeability, and vasodilation. Cellular effects comprise DNA repair inhibition, protein denaturation, and upregulation of heat shock proteins. (reprinted with the permission from [23]).

## 2.2. Ferromagnetic and ferrimagnetic materials

Iron, nickel, and cobalt are the most pertinent examples of ferromagnetic materials. Some classes of amorphous metallic alloys and rare earth compounds are also known as ferromagnetic materials [24]. Ferrites are the most important ferrimagnetic materials having the spinel configuration with the common chemical formula  $AB_2O_4$  [25]. The spinel structure consists of a cubic close-packed arrangement of oxygen anions, with A and B cations placed in two different crystallographic sites with tetrahedral and octahedral oxygen coordination, respectively. The spinel configuration includes 8 A-sites and 16 B-sites. As the A-sites are occupied by A cations and the B-sites are occupied by B cations, known as “normal spinel”. If the A-sites are fully occupied by B cations and the B-sites are randomly occupied by A and B cations, the structure is “inverse spinel” [26]. In most spinels, the cation distribution retains a middle degree of inversion where both sites hold a fraction of the A and B cations. In ferrites, the common formula may be presented as  $QFe_2O_4$ , in which Q is a bivalent cation and iron is the trivalent cation [27]. Complex oxide compounds with dissimilar crystal structures may similarly be ferrimagnetic, for example, the hexagonal ferrites and garnets [28]. Hexagonal ferrites have a crystal structure similar to the cubic inverse spinel, but with a hexagonal symmetry. The chemical formula of these materials could be shown by  $AB_{12}O_{19}$ , in which A is a bivalent cation such as Ba, Sr, Pb, and B is a trivalent cation such as Al, Cr, or Fe [29, 30]. The two most public examples of the hexagonal ferrites are  $BaFe_{12}O_{19}$  and  $PbFe_{12}O_{19}$ .

Magnetic nanoparticles produced by different methods such as micelles and co-precipitation have appealed large research attention in current years [31, 32]. These structures showed to be suitable for providing manageable particle size and morphology, as well as for

attaining narrow particle size distribution. To assure homogeneous dispersion of magnetic nanoparticles in liquid suspensions, the synthesis conditions have been properly tailored. Additional surface functionalization has been used for this purpose, like coating with various materials including organic polymer (e.g. chitosan, polyethylene glycol), oxides (e.g. silica, alumina) or metals (e.g. gold, silver) [31-34].

Furthermore, nano-structured magnetic crystalline phases can be obtained by the glass-ceramic method much easier, with a relatively lower production cost. In this method, it is possible to obtain a wide range of magnetic crystalline phases with different chemical compositions and fine-grained microstructures [33, 34]. Glass-ceramics are fabricated by controlled crystallization of starting glasses produced via melt-quenching or sol-gel processes. Crystallization usually occurs in a two-step heat treatment schedule containing nucleation and growth of crystalline phases. Depending on the chemical composition of the starting glass, desired crystalline phases with relevant specific features could be precipitated during the heat treatment process. On the other hand, by controlling the heat treatment parameters, such as heating rate, soaking temperature and time, it is possible to obtain the targeted microstructure with a uniform distribution of crystalline phases in the residual glass matrix.

### **3. Glass-ceramics for cancer treatment via magnetic hyperthermia**

#### **3.1. The origin of magnetic glass-ceramics for biomedical applications**

During the last few decades, numerous types of glasses and glass-ceramics have been developed for clinical applications due to their exceptional characteristics, such as biocompatibility, bioactivity, osteoconductivity, and osteo-productivity. When this class of

biomaterials implanted in the body, the precipitated apatite layer on their surface usually leads to the formation of chemical bonds between the implanted biomaterial and the living tissue [35]. The development of magnetic glass-ceramics with acceptable bioactivity has recently received much attention as thermo-seed materials in cancer treatment (especially in the case of deep-seated bone tumors). In magnetic bioactive glass-ceramics, magnetic crystalline phases generate heat under an external altering magnetic field and the residual glass matrix is responsible for bioactivity.

Generally, these deep-regional tumors are effectively destroyed when heated up to 45 °C, without any significant damage to the neighboring normal tissues [36]. Magnetic glass-ceramics implanted around cancerous bone tissues produce sufficient heat by the magnetic loss. The generated heat as a result of magnetic loss is influenced by several features such as magnetic properties of the material, amount of magnetic crystalline phases, strength and frequency of the applied altering magnetic field, the glass-ceramic microstructure, and etc. [10, 11, 37]. As mentioned previously, glass-ceramics are conventionally prepared by heat treatment of a starting glass. Therefore, the type and size of the crystallized phases are extremely dependent on the heat treatment parameters. Since the synthesis method of magnetic glass-ceramics is very effective in terms of magnetic properties, other synthesis routes like sol-gel have been also examined in recent years [37, 38]. It is known that sol-gel technique can intrinsically produce controllable size and distribution of the particles.

*In vitro* bioactivity of magnetic bioactive glass-ceramics has been commonly evaluated by examining apatite formation ability in contact with simulated body fluids (SBF). It is confirmed that glass-ceramics are able to bond to living hard tissues through the formation of an apatite

layer after SBF immersion [39]. The magnetic properties of this class of biomaterials have been investigated using vibrating sample magnetometer (VSM) at room temperature. Generally, the magnetic hysteresis loops of glass-ceramics evaluated using two different high ( $\geq 10$  kOe) and low (500 Oe) magnetic field intensities. The first magnetic field value is sufficient to measure saturation magnetization. Low-field measurements are suitable for clinical laboratory conditions [10]. Moreover, magnetic heat generation or calorimetric measurements of magnetic glass-ceramics are typically performed using a magnetic induction furnace at a magnetic field of about 500 Oe ( $\sim 400$  kHz) [8, 11].

Overall, magnetic bioactive glass-ceramic can not only be used for the cancer hyperthermia but also as a bone substitute biomaterials for the regeneration of damaged hard tissues [10, 40]. Owing to the balanced bioactivity and magnetic characteristics, magnetic bioactive glass-ceramics having acceptable hyperthermic features have been widely investigated. Table I summarizes major studies on the use of magnetic glass-ceramics for cancer treatment.

Table I. A research summary on magnetic bioactive glass-ceramics for cancer treatment.

Glass composition	Preparation technique	Magnetic Properties		Bioactivity/Biocompatibility evaluation	Main results	Ref.
		Saturation magnetization (emu/g)	Coercive force (Oe)			
30CaO, 30SiO <sub>2</sub> , 40Fe <sub>2</sub> O <sub>3</sub> (wt %)	melt quenching	100 (emu/cm <sup>3</sup> )	382.0 - 388.2	___ / Biocompatibility confirmed from the results of agar diffusion test with L929 cells.	The heat-generating power of ferrimagnetic glass-ceramics improved by prohibiting other crystalline phase formation and magnetite oxidization through the addition of each 1% of P <sub>2</sub> O <sub>5</sub> and B <sub>2</sub> O <sub>3</sub> .	[6]
24.5Na <sub>2</sub> O, 24.5CaO, 6P <sub>2</sub> O <sub>5</sub> , 45SiO <sub>2</sub> (wt %)	melt quenching	Up to ~ 22	2900 - 4400	The samples demonstrated a bioactive behavior in SBF (two weeks immersion). / ___	The addition of BaFe <sub>12</sub> O <sub>19</sub> (BF) improved both magnetic behavior and bioactivity of the final samples.	[36]
24.5Na <sub>2</sub> O, 24.5CaO, 6P <sub>2</sub> O <sub>5</sub> , 45SiO <sub>2</sub> (wt %)	melt quenching	Up to ~ 17	Up to ~ 5200	A hydroxy carbonated apatite layer found on the surface of all samples confirming their bioactivity, which increased with increasing of strontium ferrite content. / The samples showed no sign of toxicity in contact with human fetal osteoblastic hFOB cells	The addition of SrFe <sub>12</sub> O <sub>19</sub> (SrF) not only improved the magnetic properties of the 45S5 bioactive glass-ceramics but also enhanced the bioactivity and biocompatibility of them, especially for the highest SrF content sample (40% SrF).	[37]
45CaO, 33SiO <sub>2</sub> , 16P <sub>2</sub> O <sub>5</sub> , 4.5MgO, 0.5CaF <sub>2</sub> (wt %)	Sol-gel	4.63 - 9.72	90 - 300	The addition of Mn-Zn ferrite to the samples decreased the bioactivity behavior. / ___	Mn-Zn ferrite content had a direct relationship with the saturation magnetization and coercive force	[38]
40(FeO, Fe <sub>2</sub> O <sub>3</sub> ), 60CaO, xSiO <sub>2</sub> (wt %)	melt quenching	32	500	Addition of Na <sub>2</sub> O or combination of B <sub>2</sub> O <sub>3</sub> and P <sub>2</sub> O <sub>5</sub> to the basic composition resulted in apatite formation in SBF. / ___	Ferrimagnetic glass-ceramics in FeO-Fe <sub>2</sub> O <sub>3</sub> -CaO-SiO <sub>2</sub> system showed bioactivity, by the small addition of Na <sub>2</sub> O, B <sub>2</sub> O <sub>3</sub> and/or P <sub>2</sub> O <sub>5</sub> (3 %.wt).	[39]
41CaO, (52-x)SiO <sub>2</sub> , 3Na <sub>2</sub> O, 4P <sub>2</sub> O <sub>5</sub> , xFe <sub>2</sub> O <sub>3</sub> (x = 0, 2, 4, 6, 8 and 10 mol %)	melt quenching	0.17 - 7.95	91 - 523	___ / ___	Magnetic properties of samples varied with the processing parameters.	[41]
13.5CaO, 24.7SiO <sub>2</sub> , 13.5Na <sub>2</sub> O, 3.3P <sub>2</sub> O <sub>5</sub> , 14FeO, 31 Fe <sub>2</sub> O <sub>3</sub> (wt %)	melt quenching	18.6 - 31.5	35 - 180	The samples demonstrated a bioactive behavior in SBF (two weeks immersion). / ___	The magnetic features significantly changed by altering the melting temperature.	[42]
60Fe <sub>2</sub> O <sub>3</sub> , 14.3CaO, 10.37 ZnO, 15.32SiO <sub>2</sub> , 3B <sub>2</sub> O <sub>3</sub> (wt %)	melt quenching	23.13 - 52.13	7.21 - 95.93	___ / ___	The presence of ZnO led to the higher degree of crystallinity and improved magnetic properties.	[43]
43CaO, 43SiO <sub>2</sub> , 14Zn <sub>0.4</sub> Fe <sub>2.6</sub> O <sub>4</sub> (mol%)	melt quenching	6.7 - 38.4	10.7 - 167.6	___ / ___	The magnetic features varied with the soaking temperature and time period of applied heat treatment.	[44]
(65-x)SiO <sub>2</sub> , 20(CaO,P <sub>2</sub> O <sub>5</sub> ), 15Na <sub>2</sub> O,	melt quenching	0.41 - 19.6	44 - 204	Bioactivity increased with the increase	Ferrimagnetic contribution observed for x≥9 mol%	[45-]

$x(\text{ZnO}, \text{Fe}_2\text{O}_3)$ ( $6 \leq x \leq 21$ mol%)				of zinc-iron oxide content. / ____	(zinc-iron oxide).	[47]
25CaO, (40-x)SiO <sub>2</sub> , 7P <sub>2</sub> O <sub>5</sub> , 3Na <sub>2</sub> O, xZnO, 25Fe <sub>2</sub> O <sub>3</sub> (x=4, 6, 8, 10 wt %)	melt quenching	14.7 - 21.8	150 - 244	The samples demonstrated a bioactive behavior in SBF (three weeks' immersion). / ____	The magnetic and heat generating properties enhanced by increase of ZnO content and aligning magnetic field.	[10, 11, 40]
4.6MgO, 44.9CaO, 34.2SiO <sub>2</sub> , 16.3P <sub>2</sub> O <sub>5</sub> , 0.5CaF <sub>2</sub> (wt %)	Sol-gel	7.2	175	The addition of Mg ferrite decreased bioactivity, shown by hydroxy carbonated apatite layers (two weeks immersion). / The magnetic glass-ceramic samples showed no sign of toxicity in contact with osteoblast-like ROS17/2.8 cells (cell attachment)	Adding Mg ferrite led to the acquisition of magnetic property with a narrow hysteresis loop and a small coercive field.	[48]
(45-x)CaO, 34SiO <sub>2</sub> , 16P <sub>2</sub> O <sub>5</sub> , 4.5MgO, 0.5CaF <sub>2</sub> , xFe <sub>2</sub> O <sub>3</sub> (x = 5-20 wt %)	melt quenching	0.21 - 8.89	149 - 575	Bioactivity increased by further addition of iron content. / ____	Higher iron oxide content not only enhanced bone formation but also improved crystallization degree of magnetic phase.	[49]
25Li <sub>2</sub> O, 8MnO <sub>2</sub> , 20CaO, 2P <sub>2</sub> O <sub>5</sub> , 45SiO <sub>2</sub> (at %)	melt quenching	< 1	Up to 63	____ / ____	Among the glass-ceramics based on (Li, Mn) ferrite as the magnetic phase, only samples containing 8 at % Fe <sub>2</sub> O <sub>3</sub> showed ferromagnetic behavior at room temperature.	[50]
40Fe <sub>2</sub> O <sub>3</sub> , 15P <sub>2</sub> O <sub>5</sub> , 20SiO <sub>2</sub> , 5TiO <sub>2</sub> (wt %)	melt quenching	____	____	The glass-ceramics containing 20% metal oxides (MgO, CaO, MnO, ZnO, CeO <sub>2</sub> , CuO) showed bioactivity in SBF (within 7 to 30 days). / ____	The fabricated glass-ceramics possessed bioactivity by addition of 20 % metal oxides, such as MgO, CaO, MnO, ZnO, CeO <sub>2</sub> , and CuO. The apatite formation depended upon the type of the metal oxide.	[51]
15.9Na <sub>2</sub> O, 15.9CaO, 29.3SiO <sub>2</sub> , 3.9P <sub>2</sub> O <sub>5</sub> , 10.9FeO, 24.1Fe <sub>2</sub> O <sub>3</sub> (wt %)	concurrent sintering and crystallization	15	144	____ / ____	Glass-ceramics containing nanocrystals of magnetite, uniformly dispersed in the glass matrix and further crystallized during fast cooling of molten glass. The content of iron oxide in the glass composition showed a great influence on the magnetic behavior.	[52]
13.5Na <sub>2</sub> O, 13.5CaO, 24.7SiO <sub>2</sub> , 3.3P <sub>2</sub> O <sub>5</sub> , 14FeO, 31Fe <sub>2</sub> O <sub>3</sub> (wt %)	concurrent sintering and crystallization	26 - 33	82 - 220	The bioactivity assessment, performed by immersing the samples in SBF up to one month evidences the formation of silica gel along with precipitates rich in Ca and P after 14-28 days of immersion.	All iron ions contribute to the crystalline structure of magnetite, and uniformly distributed in the amorphous glass matrix. The magnetic hysteresis parameters strongly influenced by microstructure, which was in turn governed by melting temperature. The magnetic glass-ceramics showed slow bioactivity kinetics. The samples could be functionalized with antineoplastic drugs.	[52-55]

### 3.2. Experimental background of glass-ceramics in cancer treatment

Magnetite ( $\text{Fe}_3\text{O}_4$ ) is a representative ferrimagnetic material and the most recommended for biomedical applications. Preparation of magnetite-containing glass-ceramics has been widely reported by several researchers and not only for hyperthermia applications [56, 57].

Luderer *et al.* [58] published the first report on ferrite based glass-ceramics as thermoseeds for hyperthermia therapy in 1983. The glass-ceramics were fabricated in a ternary system of  $\text{Al}_2\text{O}_3$ - $\text{SiO}_2$ - $\text{P}_2\text{O}_5$  and contained lithium ferrite ( $\text{LiFe}_5\text{O}_8$ ) and hematite ( $\text{Fe}_2\text{O}_3$ ) as the crystalline phases; however, they were not bioactive and the heat generation of these materials was not sufficient to destroy the malignant carcinoma [58]. Therefore, ferrimagnetic thermoseeds having higher heat generating power were required.

In 1991, Ebisawa *et al.* prepared another non-bioactive ferrimagnetic glass-ceramic in which  $\text{Fe}_3\text{O}_4$  crystals uniformly dispersed in the residual glass matrix with  $\text{CaO}.\text{SiO}_2$  chemical composition [59]. They showed that  $\text{CaO}.\text{SiO}_2$  system glasses containing iron oxide could form ferrimagnetic glass-ceramics upon heat treatment at elevated temperatures. By heat treatment of the starting glass at 950 °C, a glass-ceramic containing 36 wt % of magnetite in the glass matrix of  $\text{CaO}.\text{SiO}_2$  obtained. The magnetic properties of this glass-ceramic originated from transformation of hematite to magnetite during heat treatment [59]. In the latter study [60], Ebisawa *et al.* showed that ferrimagnetic  $\text{Fe}_2\text{O}_3$ -containing  $\text{CaO}.\text{SiO}_2$  glass-ceramics could obtain bioactivity by addition of small amounts of  $\text{Na}_2\text{O}$ ,  $\text{B}_2\text{O}_3$  and/or  $\text{P}_2\text{O}_5$  to the composition of the starting glass [60]. In this regard, they studied *in vitro* bioactivity of ferrimagnetic glass-ceramics with the compositions of  $60\text{CaO}.\text{SiO}_2$ ,  $40(\text{FeO}, \text{Fe}_2\text{O}_3)$  contained 3 weight ratios of  $\text{Na}_2\text{O}$ ,  $\text{B}_2\text{O}_3$  and/or  $\text{P}_2\text{O}_5$ . They found that concurrent presence of  $\text{P}_2\text{O}_5$  with  $\text{Na}_2\text{O}$  or  $\text{B}_2\text{O}_3$  induced bioactivity



in the studied glass-ceramics [39]. It could be inferred that glass-ceramics of the FeO-Fe<sub>2</sub>O<sub>3</sub>-CaO-SiO<sub>2</sub> system could show bioactivity as well as ferrimagnetism by the small addition of certain oxides [39]. Since then, various magnetic bioactive glass-ceramics based on the CaO-SiO<sub>2</sub> glasses containing iron oxide have been reported.

### 3.3. Current research on the development of glass-ceramics for cancer treatment

Seung-Han Oh *et al.* [13], improved the heat-generating power of ferrimagnetic CaO-Fe<sub>2</sub>O<sub>3</sub>-SiO<sub>2</sub> glass-ceramics by prohibiting precipitation of undesired crystalline phases as well as magnetite oxidization to hematite during heat treatment [13]. For this purpose, crystallization temperature was fixed above 880 °C to avoid undesirable precipitation of crystalline phases such as  $\beta$ -wollastonite (CaSiO<sub>3</sub>). Furthermore, the addition of each P<sub>2</sub>O<sub>5</sub> and B<sub>2</sub>O<sub>3</sub> (1 %) to the glass composition led to the significant decrease of crystallization temperature from 1000 to 940 °C, via decreasing the glass viscosity. Since magnetite crystals can be easily oxidized above 900 °C in air, the oxide additives can be helpful to suppress the oxidation probability [13]. Moreover, a preclinical evaluation of the as-quenched and heat treated glasses using L929 cells revealed the biocompatibility of these materials [13].

In the study carried out in 2005, Leventouri *et al.* [41] prepared ferrimagnetic bioactive glass-ceramics in the system of CaO-SiO<sub>2</sub>-P<sub>2</sub>O<sub>5</sub>-Na<sub>2</sub>O-Fe<sub>2</sub>O<sub>3</sub> through a standard melt processing technique. They have shown that the magnetic properties could vary with the processing parameters which govern the structure and microstructure of these materials [41]. In another research conducted by Singh *et al.* [61], magnetic properties of glass-ceramics resulting from glasses with the composition of 41CaO, (52-x)SiO<sub>2</sub>, 4P<sub>2</sub>O<sub>5</sub>, 3Na<sub>2</sub>O, xFe<sub>2</sub>O<sub>3</sub> evaluated as a function

of  $\text{Fe}_2\text{O}_3$  content [74]. The structural study revealed the presence of magnetite nanocrystals in the heat-treated samples containing higher than 2 mol % of  $\text{Fe}_2\text{O}_3$ , besides biocompatible crystalline hydroxyapatite ( $\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2$ ) and wollastonite ( $\text{CaSiO}_3$ ) [61]. Evaluation of magnetic properties of these glass-ceramics by adding different concentrations of iron oxide and its relationship has been understood based on the variation in saturation magnetization, coercivity, and hysteresis loop. Generally, the samples with higher than 2 mol % of iron oxide demonstrated a magnetic characteristic nearly similar to the soft magnetic materials having narrow hysteresis loop and low coercive force. According to the obtained results, the coercivity of the samples decreased with the increase of  $\text{Fe}_2\text{O}_3$  content. However, saturation magnetization and the area under the hysteresis loop showed an adverse trend. Since the area under the hysteresis loop is proportional to the magnetic loss and produced heat, samples with higher  $\text{Fe}_2\text{O}_3$  content are capable to generate more heat.

Ferrimagnetic bioactive glass-ceramics belonging to the  $\text{CaO-SiO}_2\text{-P}_2\text{O}_5\text{-Na}_2\text{O-FeO-Fe}_2\text{O}_3$  system have been developed by Bretcanu *et al.* [42]. These glass-ceramics have been extensively characterized in terms of electromagnetic properties and heat generation ability, showing a very narrow magnetic hysteresis loop, typical of ferrimagnetic materials [42, 53, 62, 63]. In this research, two series of ferrimagnetic glass-ceramics were prepared through different melting procedures of both commercial and co-precipitation-derived reagents [42]. Then, the effects of melting procedure and temperature on the magnetic properties and heat generation ability of both series were compared. In both procedures, glass-ceramics were directly obtained by cooling of the molten glasses on metallic bars, without using any crystallization heat treatment. The obtained results confirmed the relevancy between magnetic properties and

microstructure/melting temperature of the ferrimagnetic glass-ceramics. For all glass-ceramics prepared through the first procedure, the crystalline phases were mainly magnetite and hematite. The crystallinity of magnetite increased with an increase in the melting temperature. The glass-ceramics obtained by the second procedure contained a higher quantity of magnetite compare to that of glass-ceramics obtained from commercial reagents [42]. The maximum amount of magnetite crystallized in the second glass-ceramic series was about 45 wt % [7]. Room-temperature magnetic measurements, performed by means of a vibrating sample magnetometer (VSM), showed higher values of saturation magnetization for glass-ceramics obtained through melting of co-precipitation-derived reagents. Similar results were also achieved for coercivity values. Furthermore, calorimetric tests showed that the samples synthesized through commercial reagents demonstrated higher values of specific power losses. The specific power loss represents the thermal energy which generates heat [42]. It has been reported that this class of glass-ceramics could also show bioactive features [7].

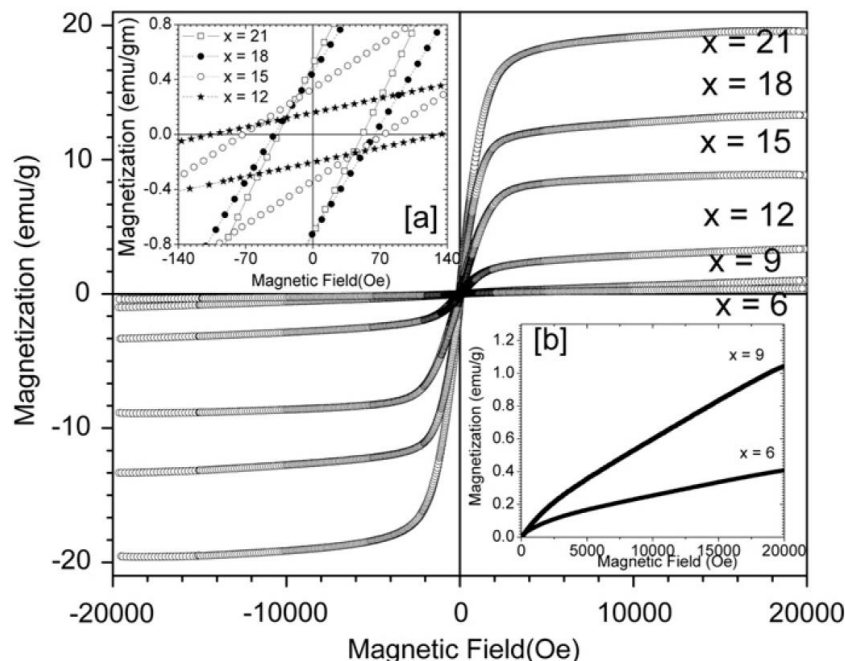
In the research by Abdel-Hameed *et al.* [43], two series of ferrimagnetic glass-ceramics in the  $\text{CaO-SiO}_2\text{-Fe}_2\text{O}_3$  system with a high quantity of  $\text{Fe}_2\text{O}_3$  (60 wt %) and small amounts of  $\text{B}_2\text{O}_3$  and  $\text{ZnO}$  were prepared. The chemical composition of one series (called FW) was similar to the composition of wollastonite, and the other series (called FH) was similar to the composition of hardystonite ( $\text{Ca}_2\text{ZnSi}_2\text{O}_7$ ). This work aimed to find a correlation between magnetic properties and chemical composition, amount of crystallized magnetite and microstructure of the examined glass-ceramics [43]. Microstructural investigations showed the precipitation of magnetite nanocrystals in the glass matrix of the as-prepared samples, without any heat treatment. The amount of crystallized magnetite in the FH series was higher than that of the FW series [43].

When subjected to the subsequent heat treatment at 800 °C for 1h, magnetite, and hematite crystallized as the major and minor crystalline phases, respectively in FW glass-ceramic series. FH glass-ceramic series had similar crystalline phases in addition to trace amount of wollastonite. According to the microstructural measurements, the crystallite size of magnetite was governed by heat treatment parameters for both glass-ceramic series [43]. The analysis of magnetic hysteresis cycles confirmed that all samples exhibited soft magnetic behavior, with small coercivity. The studied FW and FH samples had a saturation magnetization of 35.25 and 52.13 emu/g, respectively. Both samples were able to increase the temperature of distilled water to more than 40 °C under a magnetic field, being effective for destruction of tumors by magnetic heat generation of 10 W.g<sup>-1</sup> [43].

In a study by Kawashita *et al.* [44], glass-ceramic powders containing zinc-iron ferrite ( $\text{Zn}_x\text{Fe}_{3-x}\text{O}_4$ ) in a CaO-SiO<sub>2</sub> matrix were prepared by heat treatment of initial glasses with the chemical composition of 43CaO, 43SiO<sub>2</sub>, 14Zn<sub>0.4</sub>Fe<sub>2.6</sub>O<sub>4</sub> (mol %) in a controlled atmosphere. The effect of various soaking temperatures and time periods of heat treatment on the properties of the glass-ceramics were examined [44]. It was found that  $\text{Zn}_x\text{Fe}_{3-x}\text{O}_4$  phase precipitated above 700 °C, and its content and crystallite size, as well as saturation magnetization, increased with the increase of heat treatment temperature up to 1150 °C. During the heat treatment, the coercive force of these glass-ceramics firstly increased up to 1000 °C and then decreased with further increase of heat treatment temperature. By the increase of time period of heat treatment from 1 to 5h at the soaking temperature of 1150 °C, the content of the  $\text{Zn}_x\text{Fe}_{3-x}\text{O}_4$  remained constant, whereas the crystallite size and coercive force of the heat-treated powders increased. However, the saturation magnetization was decreased. Additionally, the powders

heat treated at 1150 °C for 5h showed a maximum amount of heat generation ( $12.4 \text{ W.g}^{-1}$ ). This glass-ceramic containing  $\text{Zn}_x\text{Fe}_{3-x}\text{O}_4$  could act as an effective thermoseed material in hyperthermia treatment of cancer due to the significant heat generating ability [44].

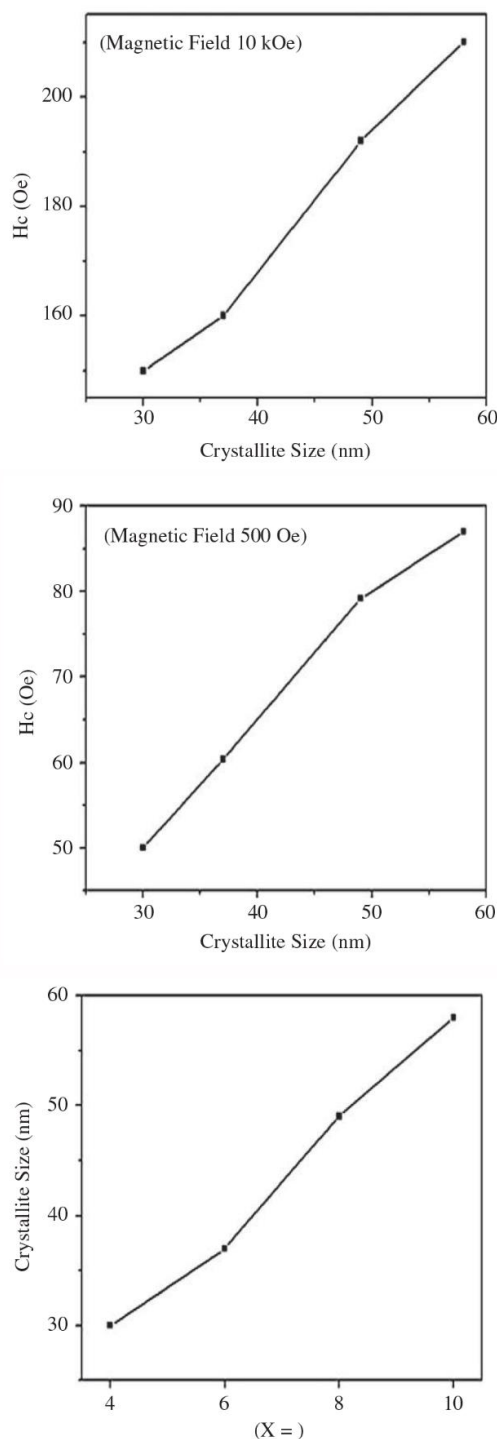
Singh and Srinivasan [45-47], have prepared a series of ferrimagnetic bioactive glass-ceramics via heat treatment of bulk pieces of glasses with the chemical composition of  $(65-x)\text{SiO}_2$ ,  $20(\text{CaO}, \text{P}_2\text{O}_5)$ ,  $15\text{Na}_2\text{O}$  and  $x(\text{ZnO}, \text{Fe}_2\text{O}_3)$  ( $6 \leq x \leq 21 \text{ mol } \%$ ) for applications in hyperthermia. From structural studies, it was found that calcium sodium phosphate ( $\text{NaCaPO}_4$ ) and zinc ferrite ( $\text{ZnFe}_2\text{O}_4$ ) were the main crystalline phases in the synthesized samples [46, 47]. Magnetic properties of the glass-ceramics originated from the amount and size of zinc ferrite nanocrystals in the microstructure [47]. Variation of magnetic properties from a partially paramagnetic to a fully ferrimagnetic and its relationship with the zinc-iron oxide content was also observed in the studied glass-ceramics [46, 47]. Magnetization curves of the glass-ceramics containing different zinc ferrite contents (shown in Fig. 3) revealed that for zinc-iron oxide up to 9 mol %, the samples exhibited both ferrimagnetic and paramagnetic behaviors; whereas, the samples having more than 9 mol % showed only ferrimagnetic features. As can be realized from Fig. 3, the magnetization curves for the samples with  $x=6$  and 9 mol % did not saturate even by applying a magnetic field of 20 kOe. However, the magnetization curves of the samples with  $x=12, 15, 18$  and 21 mol % were saturated [46]. The maximum magnetic hysteresis loss was obtained for the synthesized glass-ceramics having a higher amount of zinc ferrite in the initial glass composition [47]. Moreover, biomineralization studies indicated that the samples were able to form apatite layers on the surface of the glass-ceramics as a function of zinc-iron oxide content [45, 46].



**Fig. 3.** Magnetic hysteresis loops of  $(65-x) \text{SiO}_2$ ,  $20(\text{CaO}, \text{P}_2\text{O}_5)$ ,  $15\text{Na}_2\text{O}$ ,  $x (\text{ZnO}, \text{Fe}_2\text{O}_3)$  glass-ceramics as a function of zinc-iron oxide concentration (under a magnetic field strength of  $\pm 20 \text{ kOe}$ ). (a) An expanded view of hysteresis loops. (b) The initial magnetization curves of the sample with 6 and 9 mole% zinc-iron oxide. As can be seen, the required magnetic field to reach the saturation value increases with the further addition of zinc-iron oxide content in the glass-ceramic samples. However, there is no tendency for saturation magnetization for the samples with 6 and 9 mole % zinc-iron oxide concentrations even at  $\pm 20 \text{ kOe}$  (reprinted with permission from [84]).

With the aim of developing a ferrimagnetic bioactive glass-ceramic that could bond to the living tissues in a physiological environment, Shah *et al.* [10] reported a series of samples on the basis of zinc-ferrite ( $\text{ZnFe}_2\text{O}_4$ ) for cancer treatment. The relevant glass-ceramics were prepared by quenching the molten glasses with the chemical composition of  $25\text{CaO}$ ,  $(40-x)\text{SiO}_2$ ,  $7\text{P}_2\text{O}_5$ ,  $3\text{Na}_2\text{O}$ ,  $x\text{ZnO}$ ,  $25\text{Fe}_2\text{O}_3$  ( $x = 4, 6, 8, 10$ ) that consequently heat-treated at  $1100^\circ\text{C}$  [10]. Microstructural analyses revealed the presence of three prominent crystalline phases including zinc ferrite, wollastonite and hydroxyapatite [10]. In this research,  $\text{ZnFe}_2\text{O}_4$  revealed a ferrimagnetism characteristic due to the random contribution of  $\text{Zn}^{2+}$  and  $\text{Fe}^{3+}$  cations into the tetrahedral A and octahedral B sites, resulting in the formation of an inverse spinel crystalline

structure. This structure could be attributed to the rapid cooling of the material from 1100 °C which preserved the high-temperature state of the randomly distributed ions [10]. Magnetic evaluation of these ferrimagnetic glass-ceramics by VSM data showed that saturation magnetization and coercive force increased with the addition of ZnO [10]. Since the nano-sized  $\text{ZnFe}_2\text{O}_4$  crystals have shown a pseudo-single domain structure, the coercivity increased with the growth of crystals. Fig. 4 shows the dependency of coercivity on the crystallite size of zinc-ferrite as a function of ZnO content [10]. Calorimetric measurements, carried out using a magnetic induction furnace at 500 Oe magnetic field and frequency of 400 KHz, showed that the maximum specific power loss and temperature increase were  $26 \text{ W.g}^{-1}$  and 37 °C, respectively, for the sample contained 10 % ZnO [10].

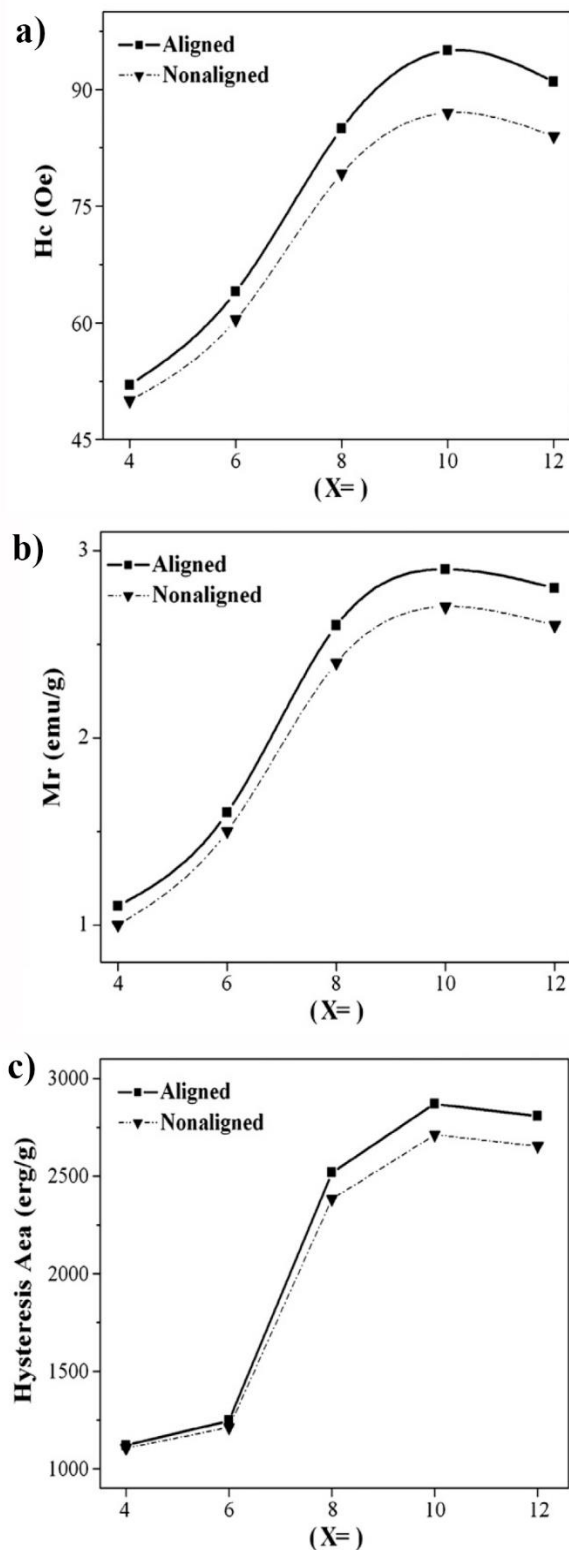


**Fig. 4.** Variations of  $\text{ZnFe}_2\text{O}_4$  crystallite size versus ZnO content in  $25\text{CaO}$ ,  $(40-x)\text{SiO}_2$ ,  $7\text{P}_2\text{O}_5$ ,  $3\text{Na}_2\text{O}$ ,  $x\text{ZnO}$ ,  $25\text{Fe}_2\text{O}_3$  glass-ceramics and coercivity force at 10 KOe and 500 Oe. As can be seen, the crystallite size increases with the further addition of ZnO. In addition, the coercivity values increase with crystallite growth of  $\text{ZnFe}_2\text{O}_4$ . Although coercivity commonly decreases by the increase of crystallite size in the multi-domain structures (owing to the facility in rotation of domain walls), when the magnetite particle size lies in the range of 10-50 nm, a single domain structure is formed which requires an increased coercivity. Since the crystallite size of  $\text{ZnFe}_2\text{O}_4$  is about 30-58 nm, it can be deduced that a pseudo-single domain structure of  $\text{ZnFe}_2\text{O}_4$  crystallites is responsible for the increase of coercivity. (reprinted with the permission from [10]).

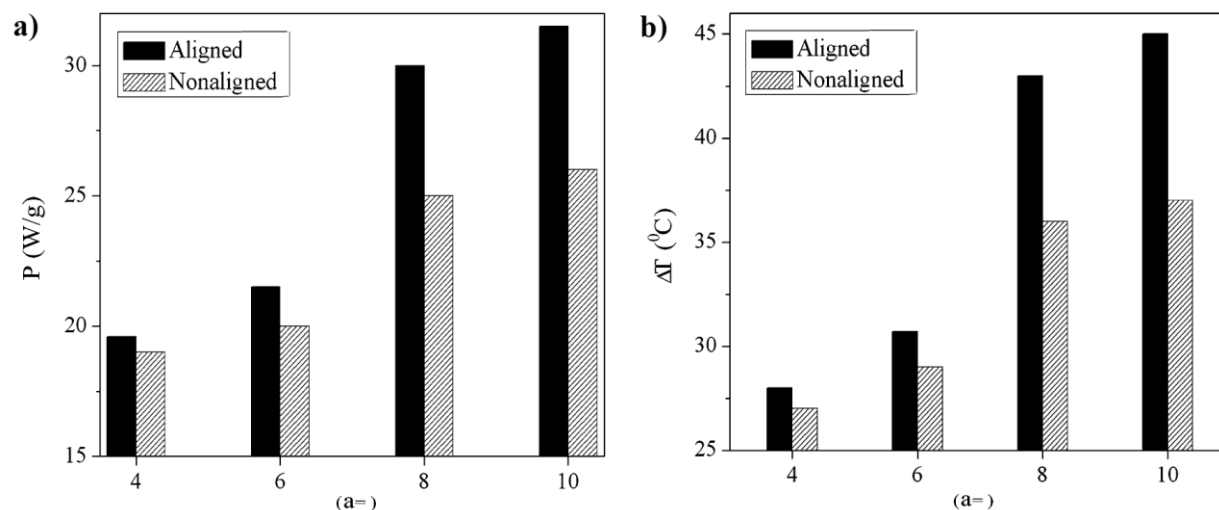


In other research [11, 40], Shah *et al.* have tried to enhance the magnetic and heat generating properties of the ferrimagnetic zinc-ferrite based bioactive glass-ceramics by control of the magnetic field. In order to induce magnetic anisotropy, after preparation of ferrimagnetic bioactive glass-ceramics in the  $\text{CaO-SiO}_2\text{-P}_2\text{O}_5\text{-Na}_2\text{O-ZnO-Fe}_2\text{O}_3$  system, the samples were heated up to 600 °C and cooled under a magnetic field. To better understand the actual performance of zinc-ferrite based glass-ceramics, the magnetically aligned samples compared with non-aligned ones [11, 40]. The VSM data taken at 10 KOe and 500 Oe (see Fig. 5) showed that the coercive force, remnant magnetization and hysteresis area increased for the aligned samples. In fact, the magnetic field applied during cooling could possibly force the magnetic domains to be aligned in the direction of the applied magnetic field, facilitating an easy axis of magnetization in the same direction. After cooling, the domains stuck aligned with the magnetic field, and stronger magnetic fields required to magnetize the sample in a different direction [11, 40]. It is implied from Fig. 5 that the variation of magnetic parameters became prominent for  $x = 8\text{--}12$  due to the higher amount of ferrimagnetic zinc-ferrite crystalline phase [11, 40]. The calorimetric studies carried out by a magnetic induction furnace at 500 Oe and frequency of 60 kHz for the aligned sample with a maximum amount of zinc-ferrite showed that the maximum specific power loss and temperature increase were  $4.4 \text{ W.g}^{-1}$  and  $6.3 \text{ }^\circ\text{C}$ , respectively [11]. Changing the frequency to 400 kHz led to a specific power loss of  $31.5 \text{ W.g}^{-1}$  and a temperature increase of  $45 \text{ }^\circ\text{C}$  after 2 min (see Fig. 6) [40]. These parameters indicated that the magnetic properties of the aligned samples greatly improved using a magnetic induction furnace. The variation of specific power loss was prominent for  $x = 8$  and  $x = 10$  related to the higher hysteresis areas [40]. Thus, the calorimetric properties and heating generation ability of zinc-ferrite based ferrimagnetic

bioactive glass-ceramics increased by cooling in an aligning magnetic field. According to the aforementioned discussion, it can be deduced that this material may produce temperatures required to destroy cancer cells when implanted in the tumorous tissue [11, 40]. The bioactivity tests confirmed the growth of precipitated apatite crystals, suggesting that the prepared glass-ceramics were bioactive for further experiments [11, 40].



**Fig. 5.** Variation of the magnetic parameters versus composition for magnetically aligned and non-aligned  $25\text{CaO}$ ,  $(40-x)\text{SiO}_2$ ,  $7\text{P}_2\text{O}_5$ ,  $3\text{Na}_2\text{O}$ ,  $x\text{ZnO}$ ,  $25\text{Fe}_2\text{O}_3$  glass-ceramics, (a) Coercive force, (b) Remnant magnetization, and (c) hysteresis area. As can be seen, the variation of magnetic parameters became prominent for  $x=8-12$  due to the higher amount of ferrimagnetic zinc-ferrite crystalline phase. (reprinted with the permission from [11]).



**Fig. 6.** a) Variation of calorimetric parameters including; a) specific power loss, and b) temperature increase versus composition for magnetically aligned and non-aligned  $25\text{CaO}$ ,  $(40-x)\text{SiO}_2$ ,  $7\text{P}_2\text{O}_5$ ,  $3\text{Na}_2\text{O}$ ,  $x\text{ZnO}$ ,  $25\text{Fe}_2\text{O}_3$  glass-ceramics. It is evident that the aligned samples present higher amounts of calorimetric parameters compared to the non-aligned samples, especially for  $x = 8$  and  $10$  (reprinted with the permission from [40]).

Leenakul *et al.* prepared ferrimagnetic bioactive glass-ceramics by heat treatment of powder mixtures composed of different amounts of solid-state synthesized barium ferrite and 45S5 bioglass powder [36]. Sodium-calcium silicate ( $\text{Na}_2\text{Ca}_2\text{Si}_3\text{O}_9$ ) and barium ferrite ( $\text{BaFe}_{12}\text{O}_{19}$ ) were identified as the major crystalline phases in all heat treated samples [36]. Magnetic hysteresis loops of the prepared samples were examined in order to highlight their capability for cancer treatment via magnetic hyperthermia. It was found that the saturation magnetization increases with the rise in the content of magnetic  $\text{BaFe}_{12}\text{O}_{19}$ . Furthermore, the coercivity of the samples decreased with the increase of  $\text{BaFe}_{12}\text{O}_{19}$  content, owing to the multi-domain structure of  $\text{BaFe}_{12}\text{O}_{19}$ . On the other hand, the hysteresis loop area increased with the rise of  $\text{BaFe}_{12}\text{O}_{19}$  from 5 up to 40 wt %, under a magnetic field of  $\pm 10$  kOe [36]. *In vitro* bioactivity measurements (14 days of the immersion in SBF) confirmed that all of the glass-ceramics possessed appropriate

bioactivity with the formation of a bone-like apatite phase. In a similar trend, bioactivity also increased with the increase of  $\text{BaFe}_{12}\text{O}_{19}$  content [36]. Therefore, it can be deduced that the addition of  $\text{BaFe}_{12}\text{O}_{19}$  into the 45S5 glass composition can improve both the magnetic properties and bioactivity of the material [36].

It has been reported that strontium-doped silicate glass discs could enhance bone cell activity and promote osteoblast proliferation and alkaline phosphatase activity in a direct contact with human osteosarcoma cell line, Saos-2 cells [64]. In a study, Leenakul *et al.* developed magnetic bioactive glass-ceramics obtained from heat treatment of powder mixtures of 45S5 bioglass® and different amount of strontium ferrite ( $\text{SrFe}_{12}\text{O}_{19}$ ) [65]. All final glass-ceramic samples contained calcium silicate ( $\text{Na}_4\text{Ca}_4\text{Si}_6\text{O}_{18}$ ), strontium ferrite ( $\text{SrFe}_{12}\text{O}_{19}$ ) and iron oxide ( $\text{Fe}_2\text{O}_3$ ) [65]. These SrF-SiO<sub>2</sub>-CaO-Na<sub>2</sub>O-P<sub>2</sub>O<sub>5</sub> ferrimagnetic glass-ceramics showed wide hysteresis loops and high coercive fields indicating the basic characteristics of a hard magnetic material. The magnetic characteristics were highly influenced by the  $\text{SrFe}_{12}\text{O}_{19}$  content in such a way that the saturation magnetization, remanence, and coercivity increased with the increase of  $\text{SrFe}_{12}\text{O}_{19}$  [65]. *In vitro* bioactivity measurements illustrated the formation of hydroxyl carbonate apatite layer on the surface of all glass-ceramics confirming their bioactivity. The bioactivity also increased with the rise of the  $\text{SrFe}_{12}\text{O}_{19}$  content [65]. Furthermore, the MTT assay cytotoxicity test using hFOB cells indicated that the studied glass-ceramic samples were non-toxic for the  $\text{SrFe}_{12}\text{O}_{19}$  content of 5-40 wt % [65]. The addition of  $\text{SrFe}_{12}\text{O}_{19}$  not only improved the magnetic properties of the 45S5-based glass-ceramics but also enhanced their bioactivity and biocompatibility, especially in the case of 40 wt %  $\text{SrFe}_{12}\text{O}_{19}$  containing sample [65].

In a similar research, Abbasi *et al.* [37] added strontium ferrite ( $\text{SrFe}_{12}\text{O}_{19}$ ) to 45S5 bioglass<sup>®</sup>. First, they synthesized the 45S5 glass powder by a solid-state reaction between soda-lime-silica waste glass and reagent chemicals of calcium carbonate, sodium carbonate, and phosphorous oxide. Then, 5-20 wt % of  $\text{SrFe}_{12}\text{O}_{19}$  powder (obtained via sol-gel technique) was added to the bioactive glass powder. Finally, the ferrimagnetic bioactive glass-ceramic samples were achieved by conventional sintering method and their structural and magnetic features along with bioactivity were examined [37]. According to the phase analysis results, three main crystalline phases of sodium calcium silicate ( $\text{Na}_2\text{Ca}_2\text{Si}_3\text{O}_9$ ), sodium calcium phosphate ( $\text{NaCaPO}_4$ ), and strontium ferrite ( $\text{SrFe}_{12}\text{O}_{19}$ ) precipitated in all prepared glass-ceramics. By increasing the starting strontium ferrite in the composition, the crystallite size of  $\text{SrFe}_{12}\text{O}_{19}$  and magnetic features of the glass-ceramic samples including saturation magnetization, remanence magnetization, and coercive force values increased [37]. Moreover, the energy loss meaning the heat generated by the ferrimagnetic material increased and reached  $75.85 \times 10^3 \text{ erg.g}^{-1}$  for the sample containing 20 % wt  $\text{SrFe}_{12}\text{O}_{19}$ , which is appropriate for hyperthermia therapy [37]. In this study, the Hanks solution *in vitro* test was used to evaluate the bioactivity of the glass-ceramic samples. It was shown that the starting time for the formation of hydroxycarbonate apatite layer on the un-modified glass-ceramics was one week, while at least two weeks were required for strontium ferrite containing samples. The authors concluded that the addition of strontium ferrite to the 45S5-based glass-ceramics could possibly decrease the bioactivity due to the fact that the amount of non-bioactive phase (magnetic phase) increased by the addition of strontium ferrite [37].

In the paper published by Da Li *et al.* [48], a multi-component system of CaO-SiO<sub>2</sub>-P<sub>2</sub>O<sub>5</sub>-MgO-CaF<sub>2</sub>-Fe<sub>2</sub>O<sub>3</sub> bioactive glass-ceramics has been synthesized to which Mg ferrite added as the magnetic phase. The XRD studies showed the presence of wollastonite (CaSiO<sub>3</sub>), akermanite (Ca<sub>2</sub>MgSi<sub>2</sub>O<sub>7</sub>), fluorapatite (Ca<sub>5</sub>(PO<sub>4</sub>)<sub>3</sub>F) and magnesium ferrite (Fe<sub>2</sub>MgO<sub>4</sub>) in the final magnetic bioactive glass-ceramics. According to the magnetic characterization, these materials exhibited characteristics of soft magnets. From the *in vitro* bioactivity assessment, although the addition of Mg ferrite could possibly decrease the bioactivity of the initial glass-ceramic, a considerable amount of hydroxy carbonated apatite was still detectable on the surface of the samples in SBF after two weeks. Furthermore, the cellular and molecular experiments with osteoblast-like cells demonstrated that the magnetic glass-ceramic were biocompatible enough for biomedical applications [48].

Singh and Srinivasan [87] synthesized and characterized a series of (45-x)CaO, 34SiO<sub>2</sub>, 16P<sub>2</sub>O<sub>5</sub>, 4.5MgO, 0.5CaF<sub>2</sub>, xFe<sub>2</sub>O<sub>3</sub> (where x = 0-20 wt %) ferrimagnetic bioactive glass-ceramics. From the structural analyses, hydroxyapatite, magnetite, and wollastonite were detectable as the main crystalline phases for all the samples having iron oxide in the composition. In addition, akermanite (Ca<sub>2</sub>MgSi<sub>2</sub>O<sub>7</sub>) was observed in the samples with higher iron oxide contents. The presence of akermanite in these glass-ceramics increased their hardness and load-bearing capability. The glass-ceramic samples were also evaluated under high and low magnetic fields. On the basis of magnetic characterization, the glass-ceramics with higher iron oxide concentration were capable to generate more heat at the same magnetic field. The results also showed that bioactivity increased as a function of iron content increment [49].

Da Li *et al.* [60] added Mn-Zn ferrite to the apatite-wollastonite glass-ceramics as the magnetic phase and synthesized an innovative class of magnetic bioactive glass-ceramics. They monitored the effects of various amounts of the magnetic additive on the phase evolution, magnetic properties, and bioactivity of the glass-ceramics [38]. In the modified glass-ceramics, a new phase of  $\text{Zn}_{0.75}\text{Mn}_{0.75}\text{Fe}_{1.5}\text{O}_4$  was crystallized in addition to the apatite, fluorapatite, and wollastonite crystalline phases. Moreover, under an external magnetic field, the saturation magnetization and coercive force were respectively increased and decreased by the rise of Mn-Zn ferrite concentration from 5 to 20 wt %. The bioactivity assessment indicated that the addition of Mn-Zn ferrite could considerably decrease the bioactivity of the glass-ceramics. An apatite layer precipitated on the surface of ferrite free apatite-wollastonite glass-ceramics after one week, while apatite precipitation on the surface of the modified glass-ceramics occurred after almost one month [38].

In the research reported by Hsi *et al.* [88], different series of glasses consisting of  $25\text{Li}_2\text{O}$ ,  $8\text{MnO}_2$ ,  $20\text{CaO}$ ,  $2\text{P}_2\text{O}_5$ ,  $45\text{SiO}_2$  (at %) have been developed having different amounts (0, 4, and 8 at %) of  $\text{Fe}_2\text{O}_3$ . This research studied the crystallization behavior and magnetic characteristics of the prepared glass-ceramics [50]. The samples indicated surface crystallization behavior during heat-treatment. After 4h heat treatment at  $850^\circ\text{C}$ , lithium manganite ( $\text{LiMn}_2\text{O}_4$ ) along with silicate-based crystalline phases including  $\beta$ -wollastonite ( $\beta\text{-CaSiO}_3$ ), lithium silicate ( $\text{Li}_2\text{SiO}_3$ ),  $\text{Ca}(\text{Ca}, \text{Mn})\text{Si}_2\text{O}_6$  and lithium calcium silicate ( $\text{Li}_2\text{Ca}_4\text{Si}_4\text{O}_{13}$ ) precipitated in the  $\text{Fe}_2\text{O}_3$  free glass-ceramics. In the  $\text{Fe}_2\text{O}_3$  containing samples, the presence of  $\text{Fe}_2\text{O}_3$  in the composition led to the precipitation of (Li, Mn) ferrite phase.  $\text{Li}_2\text{FeMn}_3\text{O}_8$  crystalline phase was also identified in the sample contained 8 at % of  $\text{Fe}_2\text{O}_3$  [50]. Microscopic observations showed the homogeneous



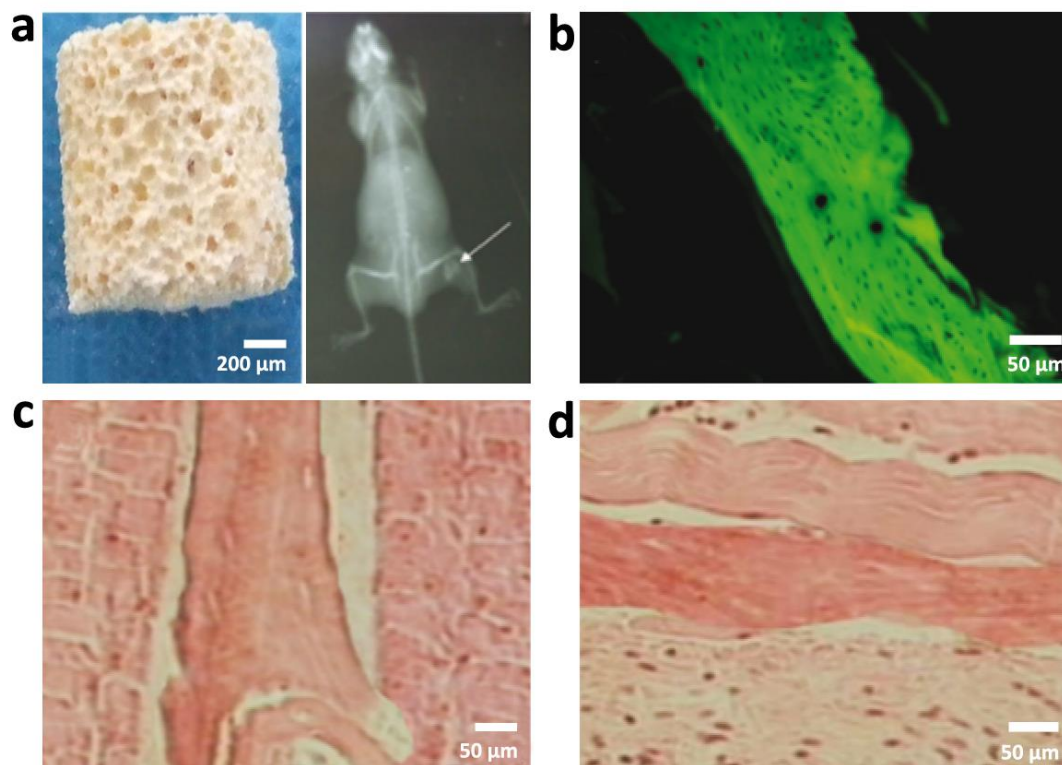
dispersion of (Li, Mn) ferrite crystals in the Si-rich matrix. On the basis of microstructural evaluations, the crystal size of (Li, Mn) ferrite could be controlled by the content of  $\text{Fe}_2\text{O}_3$  in the glass-ceramic. The average crystal size of (Li, Mn) ferrite in the glass-ceramic contained 4 at %  $\text{Fe}_2\text{O}_3$  was found to be 40 nm. As the crystal size of (Li, Mn) ferrite in the glass matrix became smaller than 40 nm, the magnetic characteristics exhibited a combination of both superparamagnetism and ferromagnetism. However, by further increase of crystal size, the magnetic behavior changed to ferro-magnetism [50].

In the research reported by Abdel-Hameed *et al* [51], the *in vitro* bioactivity of magnetic glass-ceramics belonging to a multicomponent system of  $\text{Fe}_2\text{O}_3$ - $\text{TiO}_2$ - $\text{P}_2\text{O}_5$ - $\text{SiO}_2$  with the addition of various types of metal oxides (MgO, CaO, MnO, ZnO,  $\text{CeO}_2$ , CuO) has been evaluated. The bioactivity assessment indicated the bioactivity of all the samples after immersion in SBF up to one month. Apatite formation was dependent on the type of the metal oxide. CaO, MgO, ZnO, and  $\text{CeO}_2$  added samples formed an apatite layer within one week, while MnO and CuO added samples needed 2-4 weeks. As a result, the addition of CaO or ZnO to the glass-ceramics exhibited the most promising results among the *in vitro* tested samples [51].

### 3.4. Magnetic bioactive glass-ceramics in polymer-matrix composites

An interesting way to treat bone tumors by hyperthermia is based on the utilization of composite materials, made of a polymeric matrix embedding magnetic fillers. The polymeric matrix is generally a commercial bone-cement, such as polymethyl methacrylate (PMMA) and the magnetic fillers (magnetic ceramics or glass-ceramics), as well as magnetite micro- and nanoparticles [66-70]. Kawashita *et al.* [66] reported the synthesis of a PMMA-based bone

cement embedding  $\text{Fe}_3\text{O}_4$  micro-particles. The curing parameters, compressive strength, and the heat generating ability have been reported and attributed to the amount of magnetite in the composites. In order to realize a multifunctional material, other authors reported the use of two different fillers added to the same polymeric bone cement including magnetite particles and micro-particles of a bioactive glass-ceramic or silica [67, 68]. The results obtained by the *in vivo* studies in a rabbit animal model evidenced the utility of a controlled hyperthermic treatment for bone tumors regression. Apart from the positive effects of magnetic hyperthermia on cancer treatment, there are few reports on the ability of magnetic bioactive glass-ceramics to accelerate bone formation. In this regard, Li *et al.* [71] have recently proposed a novel chitosan-based tissue engineering scaffold with apatite-wollastonite-magnetic glass-ceramic particles for the enhancement of osteogenic capability in bone defects. To examine the developed scaffold *in vivo*, a series of rabbit models implanted with free scaffolds and rabbit bone marrow stromal cells (BMSCs) loaded scaffolds. The results indicated that the proposed scaffolds could potentially promote the osteogenic capability of the newly formed bone *in vivo* (see Fig. 7).



**Fig. 7.** (a) The prepared magnetic apatite/wollastonite glass-ceramic containing chitosan-based scaffolds implanted in rabbit (in a 1.5 cm bone defect). The X-ray slice of 12 weeks implanted scaffolds indicates that high-density calcified shadow is detectable in the experimental side, but not detected in the control side (indicated by the arrow), (b) Bone tissue in control side appears as green fluorescence. (c) Histological section of the implanted scaffolds shows that mature bone tissue can be detected between muscular tissues, indicating that the proposed magnetic bioactive scaffolds could potentially promote the osteogenic capability. (d) Histological section of control side indicates immature bone and cartilage tissue between muscular tissues. (reprinted with the permission from [71]).

Composite bone cements with the ability to fill bone cavities and induce local hyperthermia have been significantly developed by dispersion of magnetite nanoparticles in a PMMA-based bone cement [69]. The compressive strength of the composites was not affected by the addition of nanoparticles in the polymeric matrix. It was found that the heat generation capacity was strongly dependent both on the magnetic nanoparticles diameter and the external magnetic field parameters. The mentioned composites did not include any bioactive phase, so it could not promote bone tissue integration. In this regard, Bruno *et al.* [54] developed a bone

cement composed of a PMMA matrix loaded with the ferrimagnetic and bioactive glass-ceramic particles, previously synthesized and characterized by Bretcanu *et al.* [7]. The ferrimagnetic and bioactive glass-ceramic micro-particles have been incorporated in the PMMA polymeric matrix in different amounts (10-20 wt %), maintaining the same monomer/solid phase (PMMA/glass-ceramic) ratio of the commercial formulation. Morphological and compositional characterizations confirmed a uniform dispersion of glass-ceramic particles in the polymeric matrix as well as their good exposition at the cement surface, assuring the needed bioactive behavior of the composite material. Any signs of particle agglomeration, which can cause a detriment to the mechanical properties, were not noticed. In fact, by tailoring the size and the content of the glass-ceramic particles in the cement appropriate compressive and bending strengths were obtained, in accordance with the ISO 5833 standard required values. All the cement compositions have been also demonstrated to be able to generate heat under an external altering magnetic field. Furthermore, it has been confirmed that the power loss amplified as a function of the ferrimagnetic glass-ceramic phase and the magnetic field intensity.

The *in vitro* properties of the mentioned composite cements have been evaluated by Vernè *et al.* [72]. Leaching behavior and bioactivity of the composite cements have been evaluated in SBF for different time intervals. Since there was no evidence for iron release from the samples, no sign of toxicity could be expected in the body fluids. Morphological and compositional analyses performed after soaking in SBF showed the precipitation of hydroxyapatite after one month; thus, evidencing a suitable exposition of the magnetic glass-ceramic at the cement surface. Cytocompatibility test has been also carried out using human osteosarcoma cells MG63. Cell viability, adhesion and spreading on the composite cements were

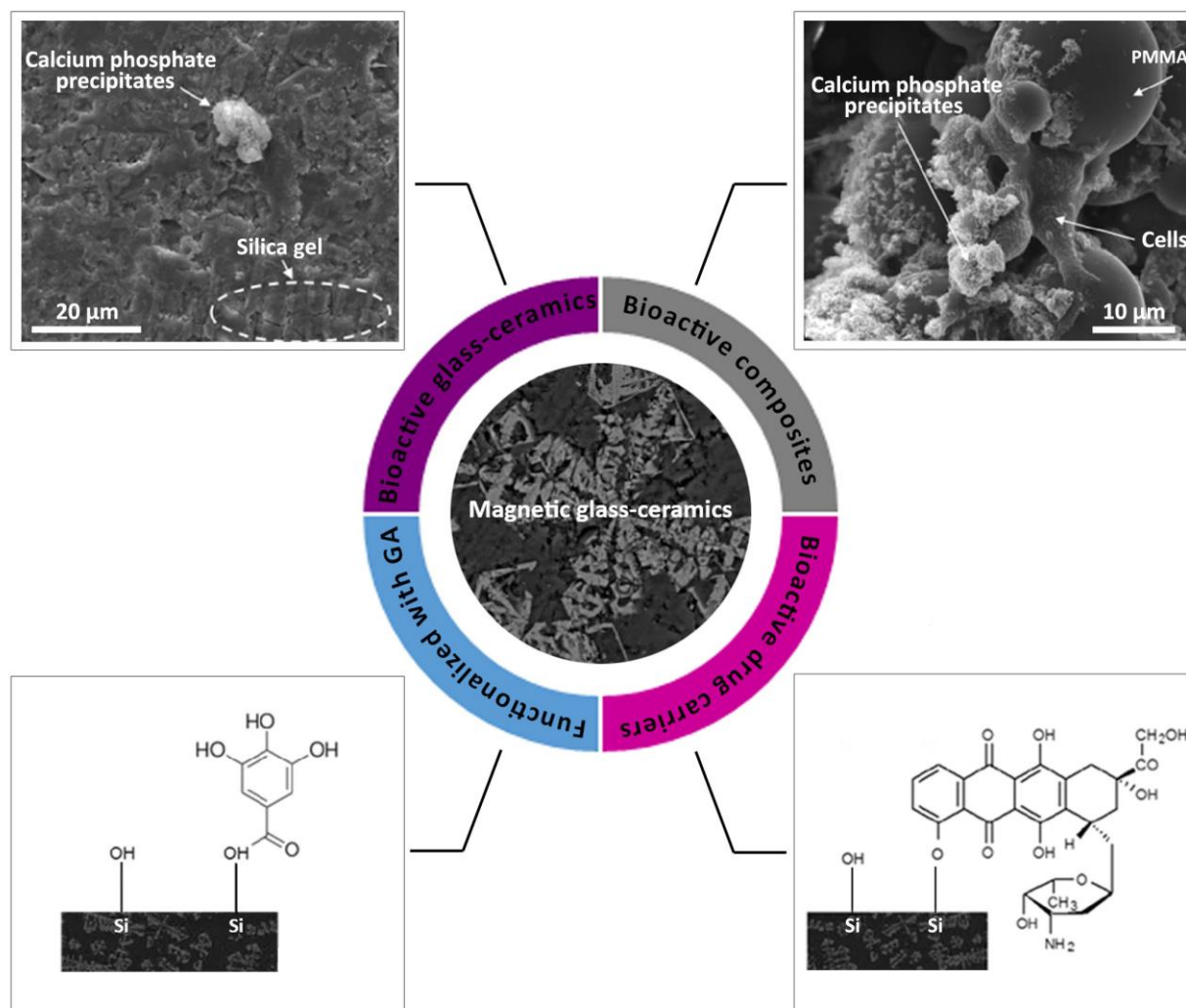
very high. Moreover, the cells demonstrated the ability to develop bridge-like structures as well as tridimensional cell multilayers after a few days of culture. A synergistic effect between cells activity and bioactivity of the ferrimagnetic glass-ceramic phase was also evidenced. Therefore, the glass-ceramics proposed by Bretcanu *et al.* [7] could be successfully used, as bioactive and magnetic fillers embedded in a polymeric matrix, for the development of a single implantable material with different therapeutic functions to treat bone tumors and associated complications.

### 3.5. Surface functionalization of magnetic bioactive glass-ceramics

The surface grafting of implantable devices with biomolecules or drugs represents a new approach for targeted local administration of therapeutic agents [73, 74]. Silica-based bioactive glass-ceramics can be surface activated in different ways in order to develop reactive sites, which in turn can bond different molecules, including antineoplastic agents [75]. Some researchers reported the surface functionalization of both inert and bioactive silica-based glasses [76-79]. In particular, the ferrimagnetic and bioactive glass-ceramics developed by Bretcanu *et al.* [7] have been surface functionalized with antineoplastic agents [55, 80]. Specifically, cisplatin and doxorubicin have been grafted after a surface activation to expose hydroxyls, functional groups. Both antineoplastic agents have been able to bind with exposed groups and their release from the glass support have been studied in different aqueous solution. The possibility of tailoring the release profile as a function of the desired therapeutic action was also investigated. Moreover, the functionalized glass-ceramic maintained its bioactivity and so it can be used as a magnetic and bioactive drug carrier. The functionalization of a ferrimagnetic bioactive glass-ceramic with gallic acid has been also investigated considering its potential applications in hyperthermic

treatment as well as the anticancer action of gallic acid [81]. In the relevant works, glass-ceramics both in bulk and powder forms have been surface grafted with gallic acid. The grafting procedure has been optimized to preserve gallic acid activity and the stability of the functionalized surface. The functionalization effectiveness has been examined with the presence and reactivity of gallic acid. The results of this research suggested that the magnetic bioactive glass-ceramics functionalized with natural polyphenols could act as promising biomaterials for bone tissue engineering and regenerative medicine in critical cancerous conditions.

Lin *et al.* [82] functionalized mesoporous bioactive glasses with folic acid in order to obtain a localized site-specific anticancer delivery system. They compared the release of a hydrophobic anticancer drug camptothecin from both unmodified and modified glass samples. The results revealed a sustained-release pattern of camptothecin, with a greater cytotoxicity behavior compared with the unloaded samples. The authors explained that the increased cytotoxicity for the loaded samples was due to the enhanced cellular uptake of the anticancer drug delivery vehicles mediated by the folic acid receptor. They concluded that the use of functionalized mesoporous bioactive glasses could be taken into the consideration as an appropriate strategy for the delivery of anticancer drugs. Fig. 8 resumes different potential applications of magnetic glass-ceramics developed by Verné *et al.* [80] ranging from composites to highly specialized functionalized systems.



**Fig. 8.** Magnetic bioactive glass-ceramics of the  $\text{SiO}_2\text{-Na}_2\text{O-CaO-P}_2\text{O}_5\text{-FeO-Fe}_2\text{O}_3$  multicomponent system and its potential applications as magnetic bioactive monoliths, bioactive magnetic composites, gallic acid (GA) functionalized glass-ceramics and magnetic bioactive drug carriers. (partially reprinted with the permission from [80])

#### 4. Mesoporous glasses for anti-cancer drug delivery

Nanoparticles are one of the most favorable alternatives for enhancing the delivery of bioactive materials with the ability to enhance their therapeutic effectiveness [83, 84]. Though nanoparticles fall in the range of 1-100 nm [85], they also contain sub-micron particles smaller than 1000 nm [86, 87]. Glass nanoparticles could be obtained from both melt quenching and sol-

gel techniques [88-92]. Melt-derived nanoparticles can be obtained from flame synthesis. In this method, starting materials rapidly melt and change to glass particles through the main flame stream [93]. The sol-gel method provides the possibility to obtain various nanoparticles at room temperature via polymerization of a sol containing compositional precursors [94, 95]. The sol-gel process has shown a suitable flexibility in which bioactive glasses could be obtained as mesoporous powders, monoliths or nanoparticles [96]. If the sol-gel process performed under simple conditions, well-defined mesoporous bioactive glass nanoparticles can be synthesized for specific applications such as anti-bacterial [97] and cancer drug delivery applications [98].

Controlled drug delivery is an important strategy for the effective treatment of various cancers [99]. Mesoporous bioactive glasses have been recently found as appropriate platforms for target-specific drug delivery applications in cancer treatment. One of the merits of these materials is that they can be also used in bone repair and regeneration as bone fillers when patients suffer from bone cancers that require to remove the part of the bone tissue. As a drug carrier, these materials benefit from a couple of advantages such as high biocompatibility and appropriate stability with the ability to bond to the living tissues [100]. In order to clarify their biocompatibility, Sui *et al.* [101] evaluated biosafety of drug-loadable mesoporous bioactive glass nanospheres *in vitro* and *in vivo*. They examined bio-distribution, clearance, cellular location and systemic risk of the mesoporous bioactive glasses through  $^{45}\text{Ca}$  labeling and histological analysis. The results revealed that mesoporous bioactive glass nanospheres could not cause cellular damages and histopathological or biochemical indices abnormality. The ability of mesoporous bioactive glasses for controlled release of imatinib (IMT), an anti-cancer drug, and its inhibitory effects on cancer cells *in vitro* has been assessed by Shoaib *et al.* [102]. They successfully loaded



IMT into a series of sol-gel prepared mesoporous bioactive glass with the loading efficiency of 77.59%. The drug loading concentration (0.2-1.0 mg/mL), as well as release kinetics, were adjusted by controlling the pH (4.4 to 10.4). They showed that the maximum drug release was about 81% during a time period of 250h at a pH of 4.4. Furthermore, *in vitro* assays confirmed that this system was a proper approach having considerable inhibitory effects on the viability of the MG-63 osteocarcinoma cancer cells (at 12.19  $\mu\text{g/mL}$  of samples). In another study, Wang *et al.* [103] studied the biological activity and doxorubicin release of mesoporous bioactive glass nanospheres. They could successfully load the anticancer drug doxorubicin into the mesoporous bioactive glass nanospheres with an encapsulation efficiency of 63.6%. Similar to other researchers, they noted that the drug release and encapsulation capability of the mesoporous bioactive glass nanospheres could be greatly influenced by the mesoporous structure as well as local pH environment. It is expected that this strategy plays an important role in the future of different cancers, with the development of innovative applications of mesoporous bioactive glasses in the treatment of different hard and soft tissues and organs.

## 5. Concluding remarks and future perspectives

Recently, magnetic nanoparticles have appealed much consideration as very favorable candidates for an extensive range of applications in cancer treatment [104, 105]. The production of magnetic nanoparticles via the glass-ceramic method has also been the focus of many works [33]. Along with their well-known benefits, like the ease of preparation and the financial concerns, glass-ceramics are also very suitable to obtain controlled microstructures. The glass-ceramic method has previously been used to synthesize some ferrite nanoparticles like  $\text{Fe}_3\text{O}_4$  and  $\text{ZnFe}_2\text{O}_4$  [10, 106]. The most favorable uses of these soft magnetite nanoparticles are in

emerging biomedical applications, such the magnetic drug targeting, magnetic separation of leukemia cells from the blood, magnetic hyperthermia, and contrast agents in MRI process [107]. Lately, several studies showed the application of these magnetic nanoparticles for tissue engineering and regenerative medicine, indicating that such stimulations could be also helpful for tissue regeneration. In these structures, the magnetic particles attach to the cell membrane and upon the use of a magnetic field, activate the membrane and initiate some biochemical reactions within the cell, not only upholding the growth of functional bone and cartilage but also enhance tissue regeneration [108-110]. One more example is the use of magnetic liposomes (lipid vesicles, holding magnetic nanoparticles in their construction either in the lipid bilayer or in the aqueous compartment) as “vehicles” for controlled/targeted drug delivery [111]. Alternatively, in recent years, there has been a revival of attention in the field of hard magnetic particles, such as barium ferrite, synthesized by the glass crystallization method. This technique enables the precipitation of nanocrystals in the glass matrix, with a properly narrow crystal size distribution. The crystal size can be controlled by the temperature and time of heat treatment.

Lately, the progress of magnetic bioactive glass-ceramics has received much attention as a thermo-seed in hyperthermia treatment of cancer, particularly deep-seated bone tumors. Usually, these deep-regional tumors are efficiently heated and destroyed at temperatures around 42-45 °C, without the damage of neighboring normal tissues [36]. Although there are still major drawbacks to overcome, the proponents of this approach are optimistic, indicating that magnetic bioactive glass-ceramics and mesoporous bioactive glasses would be effective to treat cancerous cells. It is expected that this class of biomaterials play a critical role even in clinical applications. Comprehensive researches in materials science and cellular biology still needed to

fully understand the processes involved in the treatment of cancer cells. In addition, future *in vivo* and *in vitro* studies should systematically assess various effects of glasses and glass-ceramics on different cells. Interdisciplinary research and effective collaborations can potentially overcome major issues and make this treatment a viable option in the near future.

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**Figures captions:**

**Fig. 1.** In magnetic hyperthermia, the generated heat mainly originates from eddy currents and hysteresis losses. Altering/pulsed magnetic fields are able to induce small electric currents, in conducting tissues, proportional to the applied frequency. At very high frequencies, induced currents may generate a harmful heat in the tissues. At low frequencies (0–100 KHz), the released heat in the tissues is somewhat negligible, but the induced currents, if sufficiently strong, can possibly stimulate cells through an electrically stimulation mechanism. (partially reprinted with the permission from [20])

**Fig. 2.** (a) Different heat generation mechanisms in magnetic nanoparticles subjected to the altering magnetic field. The short straight arrows show the direction of magnetic moment. The curved arrows show the movement or change of direction, and the dash lines show the domain interfaces in multi-domain magnetic particles. The Néelian relaxation is attributed to the heat generated by rotation of discrete magnetic moments in the magnetic particles; whereas the Brownian relaxation is attributed to the heat generated by physical rotation of particles originating from alignment of magnetic moments with the applied magnetic field. (reprinted with the permission from [22])

(b) Vascular and cellular effects of hyperthermia on heated tumor tissues. Vascular effects comprise increase of blood flow, vascular permeability, and vasodilation. Cellular effects comprise DNA repair inhibition, protein denaturation, and upregulation of heat shock proteins. (reprinted with the permission from [23])

**Fig. 3.** Magnetic hysteresis loops of  $(65-x) \text{SiO}_2$ ,  $20(\text{CaO}, \text{P}_2\text{O}_5)$ ,  $15\text{Na}_2\text{O}$ ,  $x (\text{ZnO}, \text{Fe}_2\text{O}_3)$  glass-ceramics as a function of zinc-iron oxide concentration (under a magnetic field strength of  $\pm 20$  kOe). (a) An expanded view of hysteresis loops. (b) The initial magnetization curves of the sample with 6 and 9 mole% zinc-iron oxide. As can be seen, the required magnetic field to reach the saturation value increases with the further addition of zinc-iron oxide content in the glass-ceramic samples. However, there is no tendency for saturation magnetization for the samples with 6 and 9 mole % zinc-iron oxide concentrations even at  $\pm 20$  kOe (reprinted with permission from [84]).

**Fig. 4.** Variations of  $\text{ZnFe}_2\text{O}_4$  crystallite size versus ZnO content in  $25\text{CaO}$ ,  $(40-x) \text{SiO}_2$ ,  $7\text{P}_2\text{O}_5$ ,  $3\text{Na}_2\text{O}$ ,  $x\text{ZnO}$ ,  $25\text{Fe}_2\text{O}_3$  glass-ceramics and coercivity force at 10 KOe and 500 Oe. As can be seen, the crystallite size increases with the further addition of ZnO. In addition, the coercivity values increase with crystallite growth of  $\text{ZnFe}_2\text{O}_4$ . Although coercivity commonly decreases by the increase of crystallite size in the multi-domain structures (owing to the facility in rotation of domain walls), when the magnetite particle size lies in the range of 10-50 nm, a single domain structure is formed which requires an increased coercivity. Since the crystallite size of  $\text{ZnFe}_2\text{O}_4$  is about 30-58 nm, it can be deduced that a pseudo-single domain structure of  $\text{ZnFe}_2\text{O}_4$  crystallites is responsible for the increase of coercivity. (reprinted with the permission from [10])

**Fig. 5.** Variation of the magnetic parameters versus composition for magnetically aligned and non-aligned  $25\text{CaO}$ ,  $(40-x)\text{SiO}_2$ ,  $7\text{P}_2\text{O}_5$ ,  $3\text{Na}_2\text{O}$ ,  $x\text{ZnO}$ ,  $25\text{Fe}_2\text{O}_3$  glass-ceramics, (a) Coercive force, (b) Remnant magnetization, and (c) hysteresis area. As can be seen, the variation of magnetic

parameters became prominent for  $x = 8-12$  due to the higher amount of ferrimagnetic zinc-ferrite crystalline phase. (reprinted with the permission from [11])

**Fig. 6.** a) Variation of calorimetric parameters including; a) specific power loss, and b) temperature increase versus composition for magnetically aligned and non-aligned  $25\text{CaO}$ ,  $(40-x)\text{SiO}_2$ ,  $7\text{P}_2\text{O}_5$ ,  $3\text{Na}_2\text{O}$ ,  $x\text{ZnO}$ ,  $25\text{Fe}_2\text{O}_3$  glass-ceramics. It is evident that the aligned samples present higher amounts of calorimetric parameters compared to the non-aligned samples, especially for  $x = 8$  and  $10$  (reprinted with the permission from [40]).

**Fig. 7.** (a) The prepared magnetic apatite/wollastonite glass-ceramic containing chitosan-based scaffolds implanted in rabbit (in a 1.5 cm bone defect). The X-ray slice of 12 weeks implanted scaffolds indicates that high-density calcified shadow is detectable in the experimental side, but not detected in the control side (indicated by the arrow), (b) Bone tissue in control side appears as green fluorescence. (c) Histological section of the implanted scaffolds shows that mature bone tissue can be detected between muscular tissues, indicating that the proposed magnetic bioactive scaffolds could potentially promote the osteogenic capability. (d) Histological section of control side indicates immature bone and cartilage tissue between muscular tissues. (reprinted with the permission from [71])

**Fig. 8.** Magnetic bioactive glass-ceramics of the  $\text{SiO}_2\text{-Na}_2\text{O-CaO-P}_2\text{O}_5\text{-FeO-Fe}_2\text{O}_3$  multicomponent system and its potential applications as magnetic bioactive monoliths, bioactive magnetic composites, gallic acid (GA) functionalized glass-ceramics and magnetic bioactive drug carriers. (partially reprinted with the permission from [80])

### Statement of Significance:

Although glass-ceramics have not yet reached their potential in cancer therapy, research activity is significantly growing. It has been speculated that this idea and the advent of modern glass-ceramics could result in significant future advances. Undoubtedly, this strategy needs further investigations and many critical questions have to be answered before it can be successfully applied for cancer treatment. This paper reviews the current state-of-the-art, starting with current products and moving onto recent developments in this field. . According to our knowledge, there is a lack of a systematic review on the importance and developments of magnetic bioactive glass-ceramics and mesoporous bioactive glasses for cancer treatment, and it is expected that this review will be of interest to those working in this area.

**Graphical abstract:**